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Original Articles.

THE ANTIPYRETICS—ACETPHENETIDIN AND ANTITHERMIN.

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ONE of my pupils, Dr. Peter J. Martin, in his prize essay[1] has shown that kairin, hydrochinon, antipyrin and thallin reduce the heat production and heat dissipation of animals thrown into an experimental fever by puncture of the four basal heat centres. Drs. Wood, Reichert and Hare previously had utilized the discovery of Drs. E. V. Bergmann and O. Angerer,[2] that pepsin would produce fever. They studied the effect of antipyrin on this fever and found H. P. reduced more than H. D. Dr. Girard[3] has recently studied the effect of antipyrin in the same manner as Dr. Martin, by puncture of the corpus striatum. He concluded that antipyrin in physiological conditions lowers the temperature of the rabbit, that this agent efficaciously combats the hyperthermia caused by irritation of a thermic centre, that in antipyrinized animals the puncture of the caudate nucleus produced its usual result. Sawadowski[4] has also shown that antipyrin acts upon heat phenomena through the caudate nucleus, for when the copora striata were removed this antithermic had no effect.

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[1] University of Penna., 1887. Published in Therapeutic Gazette, 1887.

[2] Festschrift zur dritten Saecularfeier der Alma Maximiliana, gewidmet von der Medicinischen. Facultat Wurzburg, Band 1, 1882.

[3] Revue medicale de la Suisse Romande, No. 11, 1887.

[4] Centralblatt f. med. Wissenschaft, 1888.

In my laboratory Dr. E. W. Evans[1] has exhaustively studied the effects of antifebrin upon the heat production and heat dissipation of the normal and fevered animal. The fever was produced by deutero-albumose.

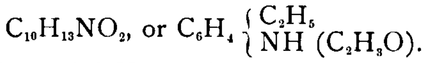
Antifebrin was found to reduce the heat production of animals normally and in a state of experimental fever. Dr Hobart A. Hare has confirmed these researches of Dr Evans.

These researches inclined me to study the latest antipyretics. In my experiments rabbits and cats were used, the drug being given by the stomach either by catheter or capsule. The insolubility of these drugs caused me to select the stomach as the medium for exhibition of the drug. Heat production and heat dissipation were measured by means of d'Arsonval's calorimeter. To produce an experimental fever, cats were used. In them the cruciate heat centres of Eulenberg and Landois were removed, which permitted the temperature to rise and to remain so till the death of the animal, The operation was performed a day or two before the exhibition of the antipyretics. No food was given to them for three days previous to the experiment.

The cruciate centre was preferred to the Sylvian for injury, as Sylvian lesions on both sides of the brain would soon cause death. How these centres act in the production of fever I have fully detailed in a previous number of this Journal (Feb., 1888). To remove the cruciate centres the skull was perforated near the median line on both sides with Pasteur's trephine. The dura mater was divided, and the cortex broken up with a blunt probe, care being taken to avoid injuring the longitudinal sinus. The effects of the drugs upon heat production and heat dissipation was not tested till an hour after their administration.

ACETPHENETIDIN.

This body is a grayish powder whose formula is



$$C_{10}H_{13}NO_2, \text{ or } C_6H_4 \left\{ \begin{matrix} C_2H_5 \\ NH \end{matrix} \right. (C_2H_3O).$$

being in fact benzol C_6H_4 in which two atoms of hydrogen are replaced by compound radicals. It has neither taste nor smell, almost insoluble in water. It dissolves in alcohol in the proportion of one in twenty. It arrests the alcoholic fermentation of grape sugar. In order to test the action of the drug on the healthy body, Dr. Georgieoski took thirty grains a day in three doses of ten grains each, separated by intervals of an hour. The only sensation produced was a slight feeling comparable to the beginning of alcoholic intoxication. No reduction of temperature was produced though the drug was taken for some days. The color of the urine was unchanged, but when a few drops of solution of chloride of iron were added to it, it gave a reddish-brown or black color; sulphate of copper gave a similar reaction. The urine was affected in half an hour after taking the dose. Observations were also made by Dr. Georgieoski upon thirty febrile patients, including cases of phthisis, typhoid, pneumonia, erysipelas of the face, acute rheumatism, quinsy, diptheria and pleurisy. A single dose of three to five grains was sufficient to lower the temperature, usually in half an hour it had gone down nearly 1° F. This reduction continued, the lowest point being reached in three to four hours after the dose had been taken. The subsequent rise which then began was very gradual, the original height not being reached for five to six hours more. As a rule, a three-grain dose reduced the temperature 1.8°, and a five-grain 3.6°. The nature of the disease seemed to have a decided influence upon the effect of the medicine; thus in typhoid, where the temperature curve generally shows great variations the drug produces a greater and more prolonged reduction than in the diseases like pneumonia, where it is less variable. This drug is also an analgesic. Acetphenetidin has a composition analogous to antifebrin.

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[1] Therapeutic Gazette, 1887.

In the following table the results upon acetphenetidin are arranged. H. P. is heat production; H. D., heat dissipation.

	Before drug.			*After drug.*		
EXP.	H. D.	H. P.	R. T.	H. D.	H. P.	R. T.
1	29.20	26.51	103	20.86	23.21	102.5
2	36.71	31.10	102.6	20.86	20.30	101.9
3	20.86	20.86	102.2	20.86	18.95	102.4
4	33.76	34.76	104.8	37.54	33.25	101.5
5	43.80	43.47	102.1	36.29	34.63	101.9
6	10.43	12.15	104.8	14.60	11.15	102.2

Increrse or decrease of H. D. after drug.	*Increase or decrease of H. P. after drug.*
— 8.34	— 3.30
— 5.85	— 10.80
.0	— 1.91
+ 3.78	— 1.51
— 7.51	— 8.84
+ 4.17	— 1.0

By an examination of the above tables and Fig. 1 it is seen that with one exception the temperature is reduced by acetphenetidin. Heat dissipation is reduced in all experiments except two, whilst heat production is diminished in all except one.

This is due to an action on the thermal centres, for when blood pressure experiments were made there was but little change in cardiac frequency. The slight fall of pressure in the arteries would not suffice to diminish heat production as much as has been shown. There was no important change in the movements of the respiratory apparatus.

ANTITHERMIN.

Its formula is

$$CH_2C(C_6H_5N\text{-}NH)\ CH_2\text{-}CH_2COOH.$$

This body has a chemical relationship to antipyrin and is composed of phenyl-hydrasin with levulinic acid. It is one of the intermediate products in the chemical production of antipyrin. It is composed of colorless crystals, of a slightly bitter taste, which causes an unpleasant grating

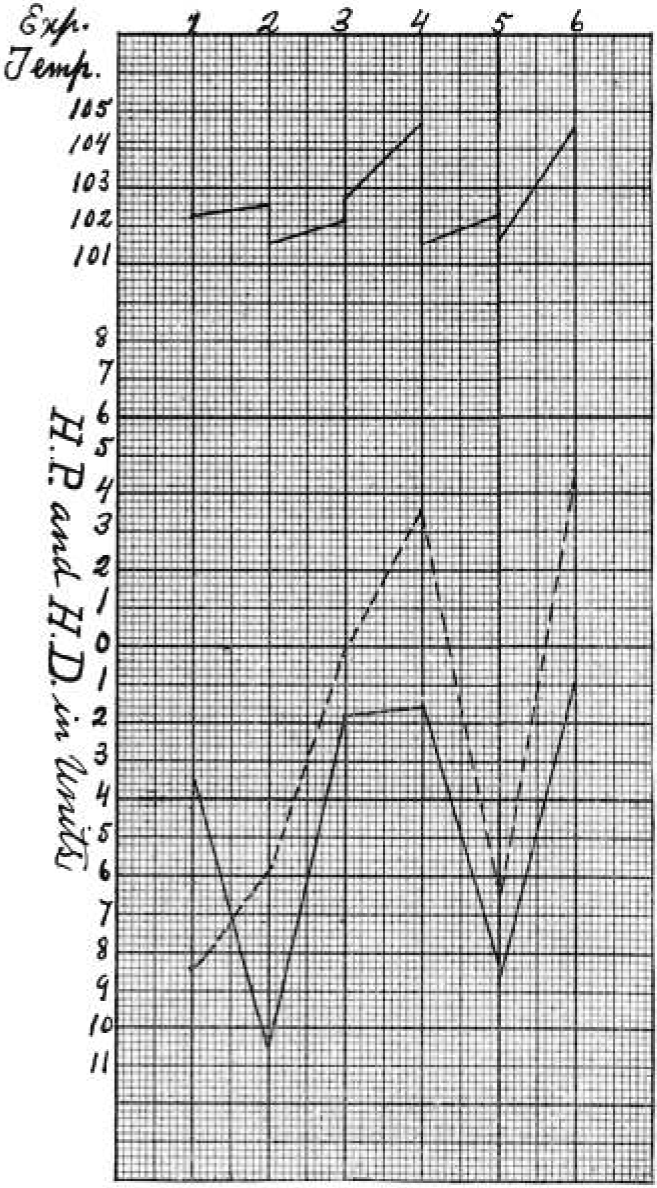
Exp.
1
2
3
4
5
6
Temp.
105
104
103
102
101
8
7
6
5
4
3
2
1
0
1
2
3
4
5
6
7
8
9
10
11
H.P. and H.D. in Units

Fig. 1.

when ground between the teeth. It is insoluble in water and but sparingly soluble in alcohol.

	Before drug.			*After drug.*		
EXP.	H. D.	H. P.	R. T.	H. D.	H. P.	R. T.
1	35.46	34.27	101.6	33.37	33.37	101.6
2	33.37	32.04	104.4	27.11	24.25	101.2
3	31.29	29.90	102.5	29.20	29.20	102.6
4	47.92	43.74	103.1	45.90	35.96	99.8
5	46.72	43.44	102.8	35.46	29.99	100.1
6	16.68	16.12	102.7	22.94	21.25	101.5

Increase or decrease of H. D. after drug.	*Increase or decrease of H. P. after drug.*
— 2.09	— .90
— 6.26	— 7.79
— 2.09	— 0.50
— 2.02	— 7.78
— 11.36	— 13.45
+ 6.26	+ 5.13

In the experiments upon antithermin, the temperature fell in all except one, and heat production and heat dissipation also were diminished in all cases save one, see Fig. 2. The cardiac frequency was not perceptibly altered by antithermin. The arterial tension was not greatly diminished. Its diminution would not account for the lessening of the heat production. No marked change was noticed in the respiration. These experiments lead to the conclusion that acetphenetidin and antithermin diminish temperature, heat production and heat dissipation as a rule.

As antipyrin acts upon the thermal centre of the corpus striatum to reduce temperature, it is highly probable that these antipyretics act in a similar way.

Appended are some of the experiments upon which the preceding statements are based.

A. T. is air temperature.

E. T., temperature of exit-tube.

R. T., rectal temperature.

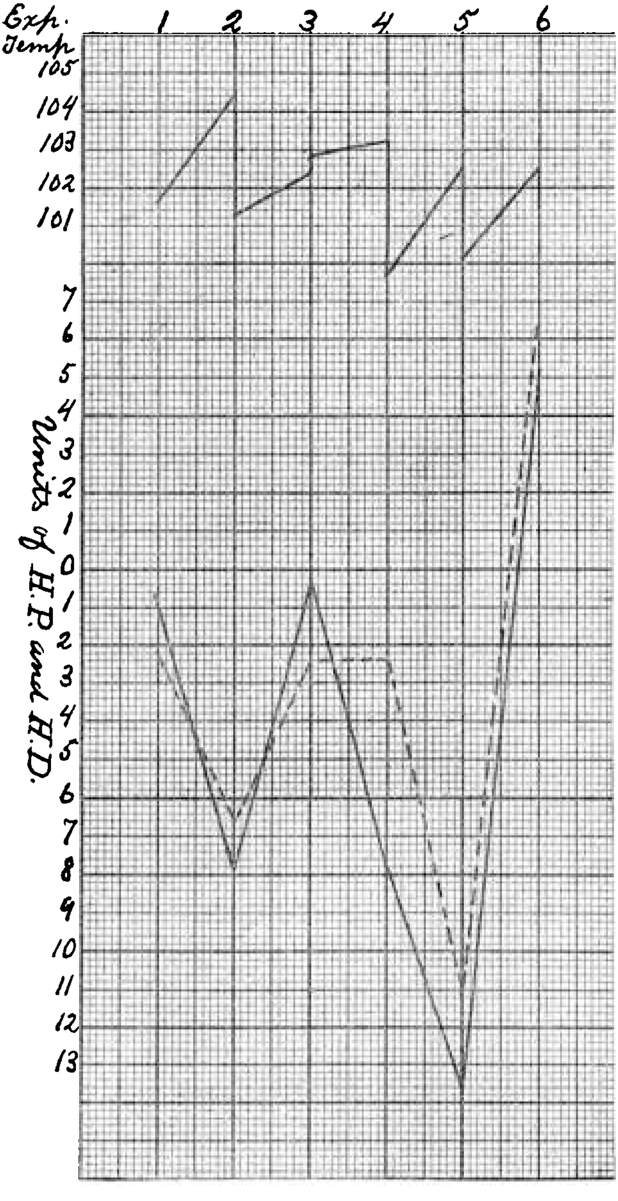
Exp.
1
2
3
4
5
6
Temp
105
104
103
102
101
7
6
5
4
3
2
1
0
1
2
3
4
5
6
7
8
9
10
11
12
13
Units of H.P. and H.D.

Fig. 2.

EXP. I.—White rabbit; wt. 4.06 lbs.

P. M.	A. T.	C. T.	E. T.	R. T.	METER.
1.30	70	73	22.1	10.30	22,424
2.30	78	73.7	24.0	102.2	22,674
		+ .7		— .8	

H. D. = 29.20. H. P. = 26.51.

2.40 Five grains of acetphenetidin by the stomach.

3.40	75.3	73.65	24.2	101.8	22,674
4.40	75.0	74.15	23.8	102.5	22,904
		+ .50		+ .7	

H. D. = 20.86. H. P. = 23.21.

EXP. II.—Rabbit, wt. 3.40.

P. M.	A. T.	C. T.	E. T.	R. T.	M.
12.10	67.8	66.8	19.5	102.65	77,980
1.10	69.0	67.68	20.4	101.00	78,336
		+ 88		— 1.65	

H. D. = 36.71. H. P. = 31.10.

1.28 Ten grains of acetphenetidin by stomach.

2.28	69.5	67.6	20.5	102.1	78,336
	69.8	68.1	20.4	101.9	78,652
		+ .5		—.2	

H. D. = 20.86. H. P. = 20.30.

EXP. III.—Rabbit, wt. 3.84.

P. M.	A. T.	C. T.	E. T.	R. T.	METER.
12.7	66.0	64.6	19.1	102.2	78,652
1.7	65.2	65.1	18.4	102.2	79,034
		+ .5		.0	

H. D. = 20.86. H. P. = 20.86.

1.25 Ten grains of acetphenetidin by the stomach.

2.52	68.2	65.1	19.1	103.0	79,034
3.52	67.0	65.6	19.2	102.4	29,284
		+ .5		— .6	

H. D. = 20.86. H. P. = 18.95.

EXP. IV.—Rabbit, wt. 3.36.

P. M.	A. T.	C. T.	E. T.	R. T.	METER.
12.32	62	61.35	16.8	104.8	79,284
1.32	64	62.15	18.3	105.3	80,975
	H. D. = 33.76.		H. P. = 34.76.		
1.34	Ten grains of acetphenetidin by stomach.				
2.40	68.8	62.4	19.0	103.1	80,975
3.40	68.8	63.3	18.5	101.5	81,126
		+ .9		— 1.6	
	H. D. = 37.54.		H. P. = 33.25.		

EXP. V.—Rabbit.

A. M.	A. T.	C. T.	E. T.	R. T.	METER.
9.58	66.8	64.3	19.1	102.1	81,126
10.58	66.5	65.35	18.8	102.0	82,290
		+ 1.05		— .1	
	H. D. = 43.80.		H. P. = 43.47.		
11.00	Ten grains of acetphenetidin by the stomach.				
12.8	66.5	65.28	18.8	102.4	82,290
1.8	69.0	66.15	19·6	101.9	83,028
	H. D. = 36.29.		H. P. = 34.63.		

EXP. VI.—Cat (cruciate fever), wt. 2.6.

P. M.	A. T.	C. T.	E. T.	R. T.	METER.
4.20	83.2	82.45	28.5	104.8	45,144
5.20	83.4	82.7	28.4	105.6	45,474
		+ .25		+ .8	
	H. D. = 10.43.		H. P. = 12.15.		
5.30	Five grains of acetphenetidin by the stomach.				
6.05	83.8	82.7	29.2	103.8	45,474
7.05	83.4	83.05	28.6	102.2	45,960
	H. D. = 14.60.		H. P. = 11.15.		

EXP. VII.—Rabbit, wt. 4.78.

P. M.	A. T.	C. T.	E. T.	R. T.	METER.
2.10	82.6	76.3	27.2	101.6	20,789
3.10	81.7	77.15	26.0	101.3	21,080
	H. D. = 35.47.		H. P. = 34.27.		

3.20 Five grains of antithermin by stomach.

4.13	81.8	77.3	29.1	101.6	21,080
5.13	81.2	78.1	26.2	101.6	21,336
		.8		.0	

H. D. = 33.37. H. P. = 33.37.

EXP. VIII.—Cat (cruciate fever), wt. 5.36.

P. M.	A. T.	C. T.	E. T.	R. T.	METER.
3.10	91.1	85.6	31.7	104.4	49,969
4.10	87.4	86·4	30.4	103.1	20,272

H. D. = 33.37. H. P. = 32.04.

4.30 Fifteen grains of antithermin by the stomach.

5.20	87.3	86.45	31.3	101.8	50,272
6.20	87.7	87.1	30.9	101.2	50,535

H. D. = 27.11. H. P. = 24.25.

EXP. IX.—Rabbit, wt. 3.84.

P. M.	A. T.	C. T.	E. T.	R. T.	METER.
1.30	81.9	78.45	27.7	102.5	21,843
2.30	83.6	79.2	26.8	102.0	22,111
		+ .75		— .5	

H. D. = 31.29. H. P. = 29.70.

2.40 Five grains of antithermin by stomach.

3.35	83.9	79.35	28.4	102.6	22,111
4.35	82.5	80.05	27.0	102.6	22,422
		+ .70		.0	

H. D. = 29.20. H. P. = 29.20.

EXP. X.—Rabbit, wt. 5.10.

P. M.	A. T.	C. T.	E. T.	R. T.	METER.
2.29	69.2	66.1	20.0	103.1	83,028
3.29	69.5	67.25	20.0	102.1	83,832
		+ 1.15		— 1.0	

H. D. = 47.92. H. P. = 43.74.

3.30 Ten grains of antithermin by capsule.

4.30	70.6	67.2	20.9	101.3	83,832
5.30	71.2	68.1	20.9	99.8	84,710
		+ .9		— 1.5	

H. D. = 45.90. H. P. = 35.96.

EXP. XI.—Rabbit, wt. 4.40.

A. M.	A. T.	C. T.	E. T.	R. T.	METER.
8.32	68.5	68.28	20.4	102.8	84,710
9.32	72.5	69.4	21.8	101.9	24,889
		+ 1.12		— .9	

H. D. = 46.72. H. P. = 43.44.

9.40	Ten grains of antithermin by capsule.				
10.33	70.8	69.4	21.5	101.6	84,889
11.33	71.7	70.25	21.8	100.1	85,756

H. D. = 35 46. H. P. = 29.99.

EXP. XII.—Rabbit, wt. 3.41.

A. M.	A. T.	C. T.	E. T.	R. T.	METER.
11.40	71.7	70.3	21.8	102.7	85,756
12.40	72.7	70.7	22.1	102.5	87,348

H. D. = 16.68. H. P. = 16.12.

1.42	73.8	70.7	23.1	102.1	87,348
2.42	73.0	71.25	22.5	101.5	87,979
		+ .55		— .6	

H. D. = 22.94. H. P. = 22.25.

EXP. XIII.—Rabbit.

P. M.	PULSE.	ARTERIAL PRESSURE.
3.15	63	120
3.25	Five grains acetphenetidin by the stomach.	
4.46	64	110
4.48	60	126
5.10	58	112

EXP. XIV.—Rabbit.

A. M.	PULSE.	ARTERIAL PRESSURE.
11.15	60	108
11.25	Five grains of antithermin by stomach.	
P. M.		
12.25	62	108
12.42	63	90